REMARKS

Remarks regarding the Oath/Declaration

1. The Applicant notes the Examiner's request for a new Declaration and certified copies of the PCT's (Paper No. 25, page 3, Section 7). The Applicant will promptly forward these documents to the Examiner once they become available.

Remarks regarding the specification:

2. A hard copy and a computer readable copy of the Sequence Listing is included herein with this amendment. The present Application also adopts the Sequence listing found in U.S. Application Ser. No. 07/750,579.

3. The specification is amended to conform to the Examiner's requirement recited in Paper 12, Sections 5, 6, 7 and 8 regarding the Figures.

4. Drawings showing amino acid sequence of antibodies and/or portions thereof have been deleted to facilitate the prosecution.

Remarks regarding the claims:

Claims 38-46 and 48-56 are pending and are rejected.

5. The Examiner rejected claims 38-46 and 48-56 under 35 U.S.C. 112, 1st paragraph, stating that "[t]he limitation of a recombinant DNA sequence encoding a human thyroid peroxidase which

is recognized by a diseased associated antibody has no clear support in the specification and the claims as originally filed." In the interest of compact prosecution, independent claims 38 and 48 have been amended to identify that the "disease associated antibody" is an antibody associated with thyroiditis (claims 38 and 48), for example Hashimoto's thyroiditis (new claims 58 and 59). Please see page 5 of the specification for support.

6. The Examiner rejected claims 38-46 and 48-56 under 35 U.S.C. 112, 2nd paragraph, for being indefinite. In the interest of compact prosecution, the Applicant is amending the claims to further clarify their metes and bounds. Independent claims 38 and 48 is amended to indicate that the human thyroid peroxidase is one which can be recognized by an antibody associated with thyroiditis (claims 38 and 48), for example Hashimoto's thyroiditis (new claims 58 and 59). Please see page 5 of the specification for support.

7. The Examiner rejected claims 38-46 and 48-56 under 35 U.S.C. 102 (b) over Libert et al. Libert et al. does not anticipate the present invention because Libert et al. discloses a full length human thyroid peroxidase, whereas the present claims are directed to truncated human thyroid peroxidase.

8. The Examiner rejected claims 38-46 and 48-56 under 35 U.S.C. 103 (a) as being obvious over Rose et al. The Examiner alleges that Rose et al. "teaches that antibodies that bind to the full length protein may also bind to the truncated, secretable variant...Thus it is clear that the recombinantly made truncated and secretable form of the transmembrane protein retains its structure as well as its ability to bind antibodies bound by the full length protein."

The Examiner has not established a case of *prima facie* obviousness with Rose et al., alone or in combination with other references, for example, EP 0139417, regarding the claims at issue. For example, the Examiner has not shown that one of ordinary skill would have expected that there

would be a likelihood of success in arriving at the claimed invention in light of the cited references.

The Rose et al. reference cited is not helpful to one of ordinary skill to predict that there is a likelihood of success at achieving the claimed invention. One of the reasons for this is that the protein under examination in the Rose et al. reference is so different from the protein of the present invention. For example, the Rose et al. reference deals with a G-protein, which is found on the intracellular side of a cell membrane; whereas, the present invention deals with a hTPO, which is found on the extracellular side of a cell membrane. A membrane bound intracellular protein with a hydrophillic COOH terminus, such as the G-protein, and a membrane bound extracellular protein with a hydrophilic COOH terminus, such as the hTPO, undergo very different biogenesis. For example, the topogenic sequence of amino acids of the G-protein must act in such a way as to orient the amino terminus of the G-protein, the bulk of the G-protein, to be inside the cell. The topogenic sequence of amino acids of the hTPO must act to the contrary to orient the amino terminus, the bulk of the hTPO, to the outside of the cell. Furthermore, proteins on the inside and outside of a cell usually start off being on the opposite sides of an endoplasmic reticulum.

To be able to apply findings of Rose et al. toward the present invention, one would have to first assume that a transmembrane intracellular protein and a transmembrane extracellular protein have the same biogenesis--which they do not, as discussed above. Then, one would have to also assume that removal of a transmembrane domain of an intracellular protein has the same effect as the removal of a transmembrane domain of an extracellular protein. These assumptions are at best tenuous. For example, a protein having the bulk of its polypeptide primarily inside the endoplasmic reticulum would most likely end up in the endoplasmic reticulum when its transmembrane region is truncated. However, a protein with the bulk of its polypeptide facing the cytosol would most likely be released into the cytosol as its transmembrane region is cleaved. As such, a transmembrane intracellular protein, such as a G-protein, and a transmembrane extracellular protein, such as a hTPO are significantly different, and may follow completely different pathways once their transmembranes are deleted. Therefore, the Rose et al. reference does not help predict that there would be any

likelihood of success of the present invention.

Even if one of ordinary skill in the art were to assume that the G-protein in Rose et al. and the hTPO protein of the present invention are sufficiently similar, a showing that a removal of the COOH terminus in the G-protein makes a secretable truncated G-protein does not necessarily suggest that a removal of the COOH in the hTPO also makes a secretable hTPO. That is, there is no likelihood of success that a removal of the transmembrane domain of a hTPO would make it secretable. Additionally, Rose et al. stated in their Summary that the truncated G-protein is secreted "**slowly**." Such statement, if anything, casts a shadow of doubt over any prospect of being able to successfully create a secreted truncated hTPO. (Please note that substantially all of the truncated hTPO's of the present invention are secreted as soon as they are synthesized. This fact suggests that the truncated hTPO's of the present invention are secreted rather "quickly."). Furthermore, although in 1982 Rose et al. showed that the removal of a transmembrane domain causes the G-protein to be secreted, for years it was shown that a secreted thyrotropin receptor (TSHR) CANNOT be produced by simply removing its transmembrane portion. See Chazenbalk et al., *The Journal of Biological Chemistry* 272 (30):18959-18965 (1997). In fact, even the courts have recognized that chemical and biological art, such as the present invention, are "unpredictable." That is, having achieved a particular result with one system does not necessarily mean that a comparable result will be observed with a different though analogous system. See, for example, *Genentech, Inc. v. Novo Nordisk*, 108 F.3d 1361, 42 USPQ2d 1001 (Fed. Cir. 1997). As such, even if the G-protein of the Rose et al. reference is assumed to be analogous to the present hTPO, it cannot be predicted that a truncated hTPO will be secreted. Much less, the G-protein of the Rose et al. reference is not substantially similar to the hTPO (for the reasons identified above) to be analogous. Therefore, the use of the Rose et al. reference to predict the likelihood of success of the present invention is at most wishful.

In as much as the cited references, namely the Rose et al. reference, is unable to predict that there is any likelihood of success that a truncated hTPO can be secreted, it is unable to predict that the truncated hTPO may be recognized by an autoantibody. One of the primary reason for this is

that, as indicated by the court in *Genentech*, chemical and biological art are unpredictable. *Id.*

An antibody recognizes a protein by the protein's very specific three dimensional structure. Therefore, to predict with any likelihood of success that an antibody will recognize a particular protein, the first task is to be able to determine what the three dimensional structure of that protein may be. However, *protein chemistry is very unpredictable and the three dimensional conformation of a protein may unpredictably change upon alterations to the primary amino acid sequence of the protein.* There is no reference at the time of the invention teaching that it is possible to predict with any certainty the three dimensional structure of a protein from its primary structure. In fact at about the same time as the filing of this application, Bowie et al. published an article stating to the contrary. Bowie et al. stated that to "predict structure from sequence...and subsequently to infer detailed aspects of function from the structure...[is] extremely complex, and it seems unlikely that either will be solved in an exact manner in the near future." *Science* (March 1990) **247**: 1306-1310 at 1306 col. 1). Furthermore, Wadsworth et al. reported that a single amino acid alteration to a thyroid stimulating hormone receptor completely alters its function, implicating that its three dimensional structure changes with the single amino acid alteration. *Molecular Endocrinology* **6**: 394-398 (1992).

EP 0139417 does not fill the deficiencies of Rose et al. In fact, EP 0139417 is an irrelevant reference altogether. For example, EP 0139417 discloses that a truncated polypeptide encoded by the recombinant DNA has the same antigenic determinant as the full length membrane bound polypeptide. It must be emphasized that there is a significant difference between (1) using a truncated polypeptide to raise an antibody, wherein that antibody recognizes a full length peptide (EP 0139417) and (2) generating a truncated polypeptide (a recombinant hTPO) which is able to bind to a pre-existing antibody, wherein the pre-existing antibody is raised by a full length polypeptide (the present invention). Therefore, the EP 0139417 reference is not even relevant to the present invention--much less would it be useful in predicting the likelihood of success of the present invention.

Therefore, it cannot be predicted that there would be any likelihood of success that a truncated hTPO of the present invention may be secreted or recognized by a pre-existing antibody, for example an autoantibody, in light of Rose et al, alone or in combination with other references. Much less, it cannot be predicted that a truncated hTPO of the present invention may be secreted and be recognized by a pre-existing antibody.

In view of the above discussion, Applicant respectfully submits that claims 38-46and 48-56 have overcome the Examiner's rejections. Furthermore, the Applicant respectfully submits that new claims 58 and 59 are also patentable over the cited references.

It is believed that in view of the amendments and the remarks, the claims are in condition for immediate allowance. Early notice to that effect is earnestly solicited.

Respectfully submitted,

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